STORIES OF DISCOVERY

Glimpses into the Working Brain: The Development of Neuroimaging Tools to Advance Our Understanding of Addiction

There is a scene in a Sherlock Holmes story where Detective Holmes and his arch villain first meet. After looking intently at Holmes' forehead, the villain remarks, "You have less frontal development than I should have expected." This statement is an allusion to an early study of the brain called "Phrenology." Developed in the early 1790s by Franz-Joseph Gall, Phrenology hypothesized that an individual's skull directly reflected underlying brain structure and thus function. The shape of one's brain was also thought to tell you about that person's character. Phrenology reflected the state of understanding of the brain at that time – that is, using the gross shape of the skull to provide insights into both the brain and the person. Phrenology was discredited by scientific research but led to some of the first notions of how the brain and behavior were related.

Our understanding of brain function since the 18th century has advanced tremendously, although amazingly, the underpinnings of today's modern neuroimaging technologies were built on findings from that era. In 1890, the noted psychologist, William James, wrote that blood flow to the brain was related to brain function. Additionally, the seminal experimental work by the British Nobel Prize winning physiologist, Sir Charles Sherrington, demonstrated that blood flow increases in parallel with neuronal activity. These advances came about at the same time that scientists were gaining a basic understanding of how information is processed in the brain. As the world began to learn about how complex the brain actually is with its neurons, neurotransmitters and receptors, little did we realize that soon we would actually be able to see this complex structure that guides all of our thoughts, feelings, and behaviors. It was the recognition of the link between neural activity and blood flow that formed the empirical foundation for today's brain imaging methods, such as positron emission tomography and functional magnetic resonance imaging.

The hardware behind these brain imaging technologies dates back over 100 years as well. In 1895, the German physicist, Wilhelm Conrad Roentgen, discovered the X-ray, which subsequently gave medical and research science a way of visualizing the living brain through the skull. This discovery won him the first Nobel prize for physics in 1901. It was not until 1972 when the X-ray technology was further refined by Sir Godfrey Hounsfield. Hounsfield introduced the world to X-ray computed tomography (CT). The CT combines X-rays and computer imaging to create images that are more detailed than the standard X-ray. Although this advance rapidly began to change how we looked at the human brain, it still only produced anatomical pictures, or essentially "snapshots," that did little to characterize what we now know as the dynamic process of brain function. The stage, however, was now set to develop tools that could inform practitioners and researchers as to what was happening in the brain, especially in response to substances of abuse.

By the mid 1970s, positron emission tomography (PET) was developed and utilized to study various brain-based diseases and disorders, including addiction. PET was used to show the dynamics of blood flow, to measure the metabolism of glucose (the fuel for brain cell function), as well as to characterize brain receptor systems. In the early 1980s, magnetic resonance imaging (MRI) began to be used in medicine. This imaging technique takes advantage of the magnetic properties of blood itself to reveal blood flow and activity within the brain. Both PET and MRI methods have been used by researchers to provide new insights into how brain function directs human behavior.

The earliest studies using neuroimaging in humans to elucidate the biology of addiction are thought to have been conducted in the mid- to late-1980s. Up to that point, much of what was known of the biology of addiction came from animal studies. By applying these methods to addiction, we were able to gain powerful, new insights into how exposure to drugs (of abuse) changed brain structure and function. It was possible to determine which brain circuits, pathways and systems were most involved and affected by abused drugs. The delineation between the acute and chronic effects of drug exposure was now possible. Most importantly, imaging clearly helped to establish that the brain could be structurally and functionally changed by drugs of abuse. We now had the proof to definitively show that addiction is, in fact, a brain disease.

Specifically, in the mid-1980s a turning point in our understanding of drug-brain-behavior interaction in humans came with two studies using PET. This work was extremely important because neuroimaging clearly illustrated the effects of a drug of abuse in the brain of a living person. Dr. Nora Volkow and her colleagues at Brookhaven National Laboratory revealed the path taken by cocaine and where in the brain it became localized, as well as the time course of its presence in and clearance from the human brain. She literally showed us a minute by minute sequence of a person’s brain on cocaine. Importantly, this time course of cocaine’s actions in the brain was directly correlated with its pleasurable experience. Dr. Edythe London and her colleagues performed a complementary study showing the effects of cocaine on the brain functioning. For the first time, these studies revealed how the brain changed when cocaine was administered. Later studies by Dr. Hans Brieter and colleagues took advantage of the rapid imaging capabilities of functional MRI to show in a time-lapsed sequence, virtually second by second, just how quickly cocaine affects a particular area of the brain. Neuroimaging studies of addiction are now being applied to show us what, if any, long-term effects drugs may have on the brain. This approach has been particularly useful as we attempt to understand the long-term effects on the brain of drugs being used increasingly across the country such as methamphetamine and MDMA (Ecstasy). Through the use of these modern imaging techniques, we now have direct evidence in humans to support the voluminous animal literature showing a decrease in a structural component of serotonergic or brain 5-HT neurons in human MDMA users. Additionally, we are now beginning to see signs that MDMA has residual effects as well – it can impair one’s cognitive abilities. Further, these techniques can also be used to help us understand if the brain can fully recover from drug abuse and addiction. Are drug-induced brain changes permanent? Can abstinence or treatment allow the brain to change back to more normal structural and functional states? These are some of the questions we hope to be able to answer through modern science.

Thanks to one advance after another, neurobiologists can peer into the living human brain and produce images that shed new light on brain function, especially as it is related to drugs of abuse. The future holds even more promising results and new insights that will unlock many of the remaining mysteries of the brain.

MEDLINE and MEDLINEplus: A Continuing Story of Discovery

Medical practitioners and medical researchers both depend on the accumulated wisdom of those who have gone before. It was not so long ago that one could assemble this wisdom only by poring over printed bibliographies, usually the *Index Medicus*, which the NIH began publishing in 1879. Today, virtually all biomedical scientists, many health practitioners, and an increasing number of consumers use a variety of methods to search the MEDLINE database to learn about published research findings.

The pioneering MEDLINE project, begun in the early seventies, evolved from the computerized system used to produce the *Index Medicus*, which the NIH had installed in 1964. MEDLINE was the first successful marriage of a large reference database with a national telecommunications network. The eighties saw the introduction of Grateful Med, a software program created by the NIH that one could load onto a PC and, equipped with a modem and a password, search MEDLINE right from one's home, office, or laboratory. Grateful Med was eagerly snapped up not only by librarians but also by health professionals, scientists, students, lawyers, medical journalists and others, who saw the average charge of $2 per MEDLINE search as a bargain.

This, of course, is the age of the Internet and the World Wide Web. The NIH Web site is the second most heavily trafficked site in the Federal Government, and these databases account for the majority share of that use. MEDLINE searching via the Internet Grateful Med was introduced in 1996. The following year, free MEDLINE searching via the Web, began using a new system called PubMed. Now, for the first time, anyone with access to the Web could search through an immense database of references and abstracts to 11 million medical journal articles. The response was immediate and startling: from 7 million MEDLINE searches (1996), the usage climbed dramatically and now stands at 400 million searches annually.

Improvements to PubMed continue to be introduced, and today it offers a high degree of flexibility to users. For example, there are now Web links to about a quarter of the publishers represented in MEDLINE, allowing users to have access to the full text of articles referenced in the database. Where such links are not available, users may use PubMed to place an online order for an article directly from a library in the National Network of Libraries of Medicine. A popular new feature of PubMed is the ability to limit a MEDLINE search to articles about complementary and alternative medicine.

The introduction of PubMed had simplified MEDLINE searching to the point where the public encountered no difficulty at all in retrieving relevant references on any biomedical subject from the literature. Since, as it turned out, about 30 percent of all MEDLINE searches were being done by consumers, this presented the NIH with a wonderful opportunity. Why not create a service that not only will provide selective MEDLINE results that are useful to the consumer, but also link the Web user to authoritative, full-text health information. Such a service, called MEDLINE*plus*, was introduced in October 1998.

Where did such authoritative information come from? Since the NIH publishes a wealth of consumer health information based on the medical research it sponsors, it was natural to start there. Also recruited were professional medical societies and voluntary health agencies, many of which issue, without commercial or business motive, authoritative information that the public can trust. With help from members of the National Network of Libraries of Medicine across the country, NIH information specialists have selected and organized this information and extensively cross-linked it. Because the name MEDLINE had a quarter-century exposure to the health professions, and because that database was now also increasingly known to the public, the NIH called the new service MEDLINE*plus* (http://medlineplus.gov).

In the two and a half years since its introduction, the service has grown tremendously, both in terms of its coverage of health and its usage by the public. As of August 2001, MEDLINE*plus* was being consulted some 6 million times each month. The original two dozen health topics, containing detailed consumer information on various diseases and health conditions, have been increased to almost 500. Other information available through MEDLINE*plus*: medical dictionaries and an encyclopedia, detailed information about prescription drugs, directories of health professionals and hospitals, links to organizations and libraries that provide health information for the public, and preformulated searches of MEDLINE on various aspects of the health topics to find scientific articles. Recent additions to MEDLINE*plus* are interactive patient tutorials, health-related news items from the daily print media, and a new database, ClinicalTrials.gov. This last addition is especially worthy of note. ClinicalTrials.gov is a registry of some 5,500 trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases. The database includes a statement of purpose for each study, together with the recruiting status, the criteria for patient participation in the trial, the location of the trial, and specific contact information. Planned improvements for MEDLINE*plus* include an interface in Spanish and modules for special groups, such as seniors.

The task now is to ensure that these health information services are known and used even more widely. To that end, NIH is working through the eight Regional Medical Libraries and the thousands of member institutions of the National Network of Libraries of Medicine to reach into communities around the Nation. There are special outreach programs directed to African-Americans, Latinos, Native Americans, and rural populations. The taxpayer's investment in medical research will be fully repaid only when the most authoritative and understandable health information is freely available to every American.

Hearing Aids – How Basic Biology Translates into Technology to Help the Hearing Impaired

Cornell University neuroscientists knew they had one amazing fly on their hands when they tested *Ormia ochracea*, a tiny insect parasite with such acute directional hearing that it has inspired a new generation of hearing aids and nanoscale listening devices. But it wasn't until the scientists ran an experiment on a fly-sized treadmill that they fully appreciated *Ormia's* talent for sound localization. Not only can the fly match the species thought to have the best directional hearing – *Homo sapiens* – it does so with a fraction of the distance between the two ears, suggesting new strategies for miniaturization of man-made devices.

These latest findings encourage research to develop a very small and inexpensive directional hearing aid. Collaboration between neurobiologists and engineers is underway to make a directional hearing aid that would be smaller, simpler, and cost thousands of dollars less than currently available devices. Nanoscale listening devices based on the *Ormia* ear are under development at several industrial and university laboratories.

Since human ears are about 6 inches apart, we have about 10 microseconds to make the same calculation that the *Ormia* fly, with its half-millimeter head, makes in about 50 nanoseconds – two hundred times faster. Trying to mimic the *Ormia* ear in silicon, engineering groups so far have developed prototype "microphone eardrums" that function "*Ormia* -like" as predicted but at ultrasonic frequencies. Additional research will be needed to generate prototypes that detect sound in the human hearing range and that will be highly directional, fit inside the ear canal, and be affordable. Other applications of the *Ormia*-inspired silicon ear might be in robotic listening devices.

Individuals who use hearing aids often struggle to understand conversation competing with other sounds and noises in the environment. The biological lessons provided by a parasitic fly's abilities in hyperacute time-coding and localization of sound provide strategies for improved nano/micro-scale directional microphones in hearing aids. Applications of these new principles may improve the quality of life for individuals with hearing loss who depend upon hearing aids.